Remarks

Entry of the present amendment and reconsideration of this application is respectfully requested. Claims 28-43 are active in the application. Claims 28 and 37 are active and independent. Claim 43 is new. Claims 16-18 and 21-23 are pending but withdrawn. Claims 1-15, 19, 20 and 24-27 are canceled without prejudice or disclaimer.

Support for new claim 43 is found, *inter alia*, at specification page 16, lines 15-16.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

The Interview of November 5, 2009

Applicants sincerely thank Examiner Ricci and his supervisor for the courteous and helpful interview granted to Applicants' undersigned representative on November 5, 2009. At the interview, Applicants' representative was granted an opportunity to discuss the rejections with the Examiner and his supervisor. Applicants' ***statement of the substance*** of the interview is provided below, and within the remarks in reply to the rejections.

The Invention

As discussed at the interview, there was a need in the art for a freeze-dried form of methylcobalamin that could be used, *inter alia*, for the formulation of "high-concentration" methylcobalamin injections. Such high-concentration injections are especially useful to treat diseases such as, for example, amyotrophic lateral sclerosis or other peripheral nerve disorders. As explained in the background section on specification page 2, JP H10-218775 discloses the use of aqueous injections of methylcobalamin as a therapy for amyotrophic lateral sclerosis. 15-50 ml per ampoule, dissolved in ethanol, saline or a buffer. Large amounts, 0.5-1.5 mg/day, are used for treatment.

However, concentrated and freeze-dried forms of methylcobalamin do not have a good long-term stability. As mentioned in the background section on specification page 2, JP S62-38, S63-3137 and H1-132514 disclose freeze-dried multi-vitamins preparations that included methylcobalamin but there were problems with these preparations including

- storage stability of freeze-dried preparations;

- a problem with the ability to re-dissolve the dried form in multivitamin preparations;

- photo-instability of concentrated methylcobalamin preparations; and

- a difficulty in guaranteeing the sterility of aqueous solution.

The invention embodies the discovery of a chemical environment that stabilizes freeze-dried methylcobalamin. The inventors discovered that freeze-dried high concentration compositions of methylcobalamin are very stable when the crystalline state of the excipient is suppressed, and specifically when stored freeze-dried with an excipient that comprises at least one sugar that is in an amorphous state, such sugar being selected from the group consisting of glucose, fructose, maltose, lactose, sucrose and trehalose, thereby arriving at the invention. Note that it is not required that the methylcobalamin itself be in the amorphous form, although it can be. Rather, it is sufficient if a sugar component of the excipient is in the amorphous form. The freeze-dried preparation of the invention that comprises a high content of methylcobalamin has

- has excellent stability over time and
- can be used in high-concentration methylcobalamin therapy.

As shown below, the combination of the cited art does not detract from the non-obviousness of the invention.

The Art Cited in the Rejections under 35 U.S.C. § 103(a)

The First Rejection

At Office action paragraph 6, claims 28-32 are rejected under 35 U.S.C. § 103(a) are being unpatentable over:

1. Banker and Rhodes, editors, Modern Pharmaceutics, Fourth Edition., 2002, pages 394 and 399,

2. Fumihiro *et al.,* JP 62-288534,

3. Hunik, WO 2000/37669,

4. Makino *et al.,* US 4,948,788,

5. Craig *et al., J. Pharmaceut. 179*: 179-207 (1999) and

6. Kim *et al., J. Pharm Sci 87*:931-935 (1998).

The Second Rejection

In addition, at Office action paragraph 20, claims 33-42 are rejected as being unpatentable over documents 1-7 as above, as applied to claims 28-29, and also

7. FDA Guide to Inspections of Lyophilization of Parenterals (said to be available online at http://www.fda.gov/ora/inspect_ref/igs/lyophi.html as of February 28, 1997.

The Third Rejection

In addition, at Office action paragraph 26, claims 28-30, 37, 38 and 41 are rejected as being unpatentable over the abstract of *Takatoshi et al.,* JP 63-313736 (herein "Takatoshi").

The Traversal

Applicants respectfully traverse each of these rejections, and Examiner's comments thereon, and respectfully request reconsideration.

Discussion

Banker, Hunik and Fumihiro

"Banker and Rhodes" is relied on for its disclosure at page 294, col. 2 that many drugs are too unstable in an aqueous medium to allow formulation as a solution. Instead the drug is formulated as a dry powder.

Hunik is relied on for its disclosure at page 1, lines 23-26 that methylcobalamin is known to be unstable to light in isolated form and is easily transformed to hydroxycobalamin as a dry powder

As discussed at the interview, in Applicants' opinion, Banker and Hunik are simply restatements of a generic problem that "many drugs" are unstable in an aqueous medium (Banker), and of a specific problem with liquid methylcobalamin (Hunik). Neither address Applicants' problem of how to stabilize freeze-dried concentrated preparations of methylcobalamin long term.

Fumihiro is relied on for its abstract that discloses stable freeze-dried preparations comprising vitamin B_{12}. However, as discussed at the interview, Fumihiro's multivitamin compositions also require a basic amino acid for stability and contain at least nine kinds of water-soluble vitamins. Applicants' composition do not rely on the presence of a basic amino acid for stability. The artisan who read Fumihiro has no reason to omit the basic amino acid as to do so removes Fumihiro's solution to the instability problem.

Although Examiner concludes that given the above, it would be p*rima facie* obvious to formulate methylcobalamin as a freeze-dried formulation, Applicants

respectfully reply that the invention more than simply formulating methylcobalamin as a freeze-dried formulation. It is believed that Examiner recognizes this as evidenced by the subsequent inclusion of additional art, as below, in an attempt to correct the deficiencies of Banker, Hunik and Fumihiro.

Craig

Craig is relied on for its disclosure at page 202, columns 1-2, wherein it is stated that cryoprotectants are materials which are commonly added during the freeze drying process in order to afford protection of the drug from degradation, and that the most commonly used cryoprotectants are sugars. Sucrose is mentioned as one of the sugars.

As discussed at the interview, Examiner's position seems to be that even though Examiner does not cite any art showing that methylcobalamin is unstable during freezing or freeze-thawing, the art would, in fact, freeze-dry methylcobalamin because liquid solutions were unstable, and that the art would add a cryoprotectant such as one of the claimed sugars out of caution, (presumably in lieu of adding the basic amino acid of Fumihiro).

Applicants discussed that, *arguendo*, even accepting Examiner's analysis is correct (and Applicants respectfully disagree with Examiner's analysis), it appears that Examiner, in his analysis, is improperly substituting his own opinion instead of citing art-based evidence. Craig's statement that cryoprotectants are commonly added does not mean cryoprotectants are always added. Also, Examiner assumes there is an instability problem with freezing methylcobalamin that is not evidenced anywhere on the record.

Applicants do not have any data or literature that shows that methylcobalamin is stable during the initial freeze-drying process such that a cryoprotectant would or would not be useful. However, the following can be considered.

Cryoprotectants are used to protect biological tissue from freezing damage (damage due to ice formation). Also, as discussed by Craig, cryoprotectants are used to retain tertiary structure of proteins during freeze drying of biotech products, such as is discussed at Craig page 202, column 2, where it is stated that "Both of these sugars have been investigated as additives to freeze dried protein formulations . . . and liposomes. . . ."

Regarding the distinction of the invention over Craig, a main difference is that the present invention related to a low molecular weight compound, methylcobalamin, whereas Craig's discussion of cryoprotectants is discussed in the context of proteins, which are relatively much higher in molecular weight. Since methylcobalamin has a more rigid tertiary structure than that of a protein, it is believed that methylcobalamin is stable through the freeze-drying process.

Accordingly, an artisan who read Craig would still not deem it necessary to use a cryoprotectant for preparing the formulation containing methylcobalamin as asserted by Examiner. The concept of "damage" due to ice formation is not such a concern for low molecular weight compounds as it is with whole cells or large proteins having a tertiary structure. There is no evidence that it is desired or necessary to use a cryoprotectant for preparing a formulation containing methylcobalamin - there is only Examiner's unsupported opinion in this regard. In view of Craig however, Applicants respectfully

believe it is incorrect for Examiner to conclude that the artisan would automatically add a cryoprotectant during an initial freeze drying process of methylcobalamin.

Turning now to Applicants' invention, a composition for the long term storage of methylcobalamin, it can be seen that Craig discusses product stability during storage in a different section - (section 4.2.4 on page 201, col. 2). Sugars, and especially, including an excipient that contains a sugar that is in an amorphous form, are not mentioned. Instead, Craig focuses on the glass transition properties of the compound. Craig states:

> "The glass transition of the freeze dried product must be well above the subsequence storage temperature in order to prevent collapse, hence determination of T_g for the freeze dried product has important implications for storage stability."

Craig also establishes that T_g alone cannot predict long term stability for a pharmaceutical. Note the discussion that begins in column 2 of Craig page 194 - column 1 of page 195 where it is stated:

> "However, it should be stressed that storage below T_g is far from a guarantee of physical stability. . . . The relationship between T_g and the stability of glassy pharmaceuticals is therefore complex; studies comparing the stability of glassy indomethacin and phenobarbitol, both of which have similar T_g values, showed very considerable variation in stability profiles even though both were stored below their T_g values . . . . Glassy indomethacin was reported to be stable over a 2 year period at room temperature, while phenobarbitol devitrified within 1 week."

As to pharmaceutical compounds, Craig establishes that the art did not have any way to predict long term stability of the compound, much less reach a conclusion that the addition of one of the recited sugar excipient in amorphous form would provide such stability to methylcobalamin freeze-dried preparations. Remember that the invention does not require that methylcobalamin itself be in the amorphous form (although it can be). It is only the excipient that contains one of the recited sugars in the amorphous form.

Makino

Makino is relied on as disclosing a freeze-dried preparation comprising vitamin D3, which like methylcobalamin, is unstable to light (col. 1, lines 23-24), (abstract) plus an excipient, having good stability (col. 2, line 8), that may include mono/di saccharides that include: mannitol, lactose, or other sugars ((col. 2, lines 35-39)).

As discussed at the interview, Applicants note that there is no structural relationship between methylcobalamin and vitamin D3. There's no nexus or evidence that what would maintain stability during the long term storage of one would also work on the other. The disclosure of Craig establishes that even compounds with a similar T_g do not have similar long term storage properties. Therefore, no conclusions can be made based on Makino.

It was also discussed that Makino does not characterize whether any of his sugars is in an amorphous or crystalline form. This is even though at least some of the sugars disclosed by Makino, such as mannitol, can be in both a crystalline or amorphous form as taught by Kim, below. "Amorphous" is not even mentioned in Makino nor are ways to

freeze-dry in a manner that suppresses crystallization. The artisan who read Makino could only assume that it does not matter whether the excipient contains any sugar that is in an amorphous form.

Also, it was discussed that Makino's "stability" is only assessed over 30 days at 25 degrees °C (Makino table 1, col. 6). Applicants teach that the residual ratio of methylcobalamin is 95% after 60 months at 40 degrees °C, and 95% after 2 years at room temperature (page 16, lines 13-16).

At Office action page 5, Examiner concludes that it was prima facie obvious to include, as the excipient, mannitol and lactose in view of Makino's teaching of such excipients in stable freeze-dried preparations comprising light-unstable vitamins. Examiner states that the skilled artisan would have included mannitol and lactose in the recognition that degradation of "any drug" is a concern during freeze-drying and that sugars are well known excipients useful as cryoprotectants during freeze-drying to overcome this effect.

Applicants respectfully disagree. As discussed above, Craig is not as broad a teaching as Examiner has suggested. It cannot be said that sugars are well known excipients useful as cryoprotectants for pharmaceuticals based on Craig.

Also, Makino and Kim clarify that mannitol can be present in both crystalline and/or amorphous forms depending on the freeze drying procedure. Makino's silence on amorphous forms must be taken as a conclusion that for Makino, having an excipient with a sugar that was in an amorphous form did not matter. As noted at the interview, there's nothing in Makino to push the artisan specifically to amorphous forms of a sugar

that is in the excipient to solve the long term storage problem of methylcobalamin. In fact, additional art cited by the Examiner, such as Kim (below), would lead the artisan away from using the amorphous state for an excipient as Kim discloses freeze-dried mannitol that is in a crystalline state depending on the manner in which it was freeze-dried or if a co-solute was present.

Kim

The sixth art document, Kim, is relied on as disclosing freeze-dried preparations comprising mannitol and a cosolute such as sucrose or lactose to provide an amorphous excipient.

Applicants do not require co-solutes, or mannitol, so Kim actually teaches away from the invention. Kim (in the introduction) states mannitol is useful in freeze-dried pharmaceutical products because it crystallizes. Kim states there have been reports of adverse effects on stability of drugs as freeze-dried solids when the mannitol is crystallized from a system which is initially only partially crystalline.

Kim teaches away from using preparations with non-crystalline mannitol. Kim states:

> "Below the threshold concentration for crystallization, mannitol is an effective plasticizer of the lyophilized solid. This could have adverse effects on both physical and chemical stability of the product as a result of glass transition-associate mobility" (last paragraph).

Reading Kim with Makino tells the artisan to keep the mannitol in a crystalline form to avoid possible adverse effects of amorphous form on the product due to plasticization.

The FDA Guide

The seventh art document, the FDA Guide, is relied on as disclosing that one problem associated with lyophilized powders is poor solubility, increased time for reconstitution at the user stage may result in partial loss of potency if the drug is not completely dissolved, since it is common to use in-liner filters during administration to the patient. Examiner states that as taught by Craig amorphous drugs possess enhanced dissolution profiles compared to crystalline drugs (Craig p 191). Accordingly, Examiner asserts it would have been *prima facie* obvious to include methylcobalamin in an amorphous state, motivation to ensure adequate dissolution and overcome the problem associated with lyophilized drugs being provided by the FDA Guide.

In reply Applicants respectfully discussed that the FDA Guide does not cure the deficiencies of the combination of Banker and Rhodes plus Fumihiro plus Hunik plus Makino plus Craig plus Kim. The FDA Guide is no more than a statement that there can be a problem with poor solubility with lyophilized powders. It is not specific to methylcobalamin and does not suggest how to cure any such problem that methylcobalamin preparations may have.

Takatoshi

Takatoshi is relied on by itself.

Takatoshi discloses freeze-dried vitamin complex comprising 20-27% of an excipient such as lactose and a vitamin (which can be B12) wherein the pH of the solution is adjusted and freeze-dried. At Office action page 16, Examiner asserts that absent evidence to the contrary, the lactose would exist in an amorphous state.

At the interview it was discussed that Takatoshi is a multivitamin composition that requires the presence of a polyoxyethylene hardened castor oil derivative, and also a polyhydric alcohol such as glycerol. These components are not required to stabilize the compositions of the invention. By adding these additional ingredients, Takatoshi's suggests, if anything, that their combination is necessary in order to achieve the properties of his composition. Coupled with the teachings of Craig, *supra*, that establish that long term stability properties vary between compounds even if they have a similar chemical properties, it cannot be said that Takatoshi leads the methylcobalamin artisan to a suggestion to eliminate at least two of Takatoshi's required components with any expectation of success in reaching the invention.

Takatoshi teaches away from the invention. A document may be said to teach away when a person of ordinary skill, upon reading the document, would be led in a direction divergent from the path that was taken by Applicants. By the inclusion of the additional ingredients, the artisan would be led to a different path than that taken by Applicants. Moreover, the discussion above has established that the currently claimed

invention is more than an arrangement of old elements, and is based on unexpected results.

Discussion

On a preliminary note, it was noted at the interview that throughout the Office action, Examiner has statements that assert his conclusion that certain combinations that are not the invention are *prima facie* obvious. Applicants discussed Applicants' opinion that it is error for Examiner to craft the legal discussion based on conclusions that combinations that are not the invention are *prima facie* obvious.

A conclusion of whether an invention such as a combination is *prima facie* obvious, if made, cannot be based simply on the fact, whether true or not, that sub-combinations that are not the invention are *prima facie* obvious. A conclusion that an invention such as a combination is *prima facie* obvious, if made, should address the invention as a whole.

As discussed at the interview, Examiner's combination of art is intended to show that the art suggested Applicants' claimed composition for reasons other than those that led Applicants' to the invention. Specifically, it seems to be Examiner's position that, based on the combination of the cited art, the artisan not only would have desired to make a freeze-dried form of methylcobalamin but also would have added an excipient that contains a sugar that is in the amorphous state as a matter of routine.

Documents such as, for example, Craig, establish otherwise. Craig provides evidence that long term stability of pharmaceuticals is unpredictable and dependent on

chemical structure. Moreover, as discussed above, the suggestion to add a sugar during freeze drying of pharmaceutical, methylcobalamin, that has a molecular weight that is much lower than the typical protein and that has a more rigid tertiary structure than a protein, is not present in Craig.

Additionally, Examiner's attention is respectfully drawn to Roberts, *et al.,* AIChE Journal 48: 1140 (June 2002), cited as document NPL22 in the Fourth Supplemental IDS filed November 20, 2009. Specifically, at Roberts page 1143, first column, last paragraph, the authors of Roberts state:

> "The quantitative prediction of storage stability is thus not possible at the present. Understanding the dynamics of structural relaxation of the glassy matrix on the time scale of years is also a challenging problem, and one in which progress must be made before storage stability can be reliably estimated and engineered."

Thus, the art acknowledges that the quantitative prediction of storage stability is not possible in 2002 when Roberts published, and that engineering of long term stability was unreliable.

The evidence above establishes that the invention, even if characterized as a combination of familiar elements, yields more than predictable results. That is, the invention/improvement is more than the predictable use of the prior elements according to their established functions. The invention is more than a simply substitution of one known element for another to obtain a predictable result. Thus, the invention is therefor non-obvious. It is not established that excipients containing at least one of the sugars recited in the claims and in which at least one of the sugars in amorphous forms function to increase long term stability of all compounds. The teachings of the art establish that

there was not a reasonable expectation of success that the claimed compositions would increase the long term stability of methylcobalamin preparations. The combination of the cited art is silent on any way to preserve long term stability of freeze-dried high-content methylcobalamin preparations and does not detract from the nonobviousness of the claimed invention.

In an obviousness analysis, all of the limitations in a claim must be considered, and the Examiner must support his statement and conclusions with the cited art. Here, Applicants respectfully assert that Examiner relies on speculation of what some of the documents allegedly may be teaching, and substitutes his own opinion in contrast to the teachings of the cited art. Rejections on obviousness grounds cannot be sustained by mere conclusory statements.

There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. The discussion above has shown that the rational underpinning of Examiner's articulated reasoning does not support a legal conclusion of obviousness. Accordingly, *prima facie* obviousness is not established, or, if it has been established, it has been overcome.

Conclusion

Prompt and favorable consideration of this Amendment and Reply is respectfully requested. All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request

that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn.

If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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